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Randomised controlled trials of palliative care – a survey of the views of advanced cancer patients and their relatives

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ABSTRACT

Purpose: To determine if patients with advanced cancer are interested in participation in palliative care research, particularly RCTs, and the importance of demographic factors in decision making. It sought relatives' views towards supporting trial entry, and assessed if demographic factors can predict participation.

Methods: A questionnaire was developed through multiprofessional focus groups, patient and relative interviews and pilot studies. Consecutive patients known by the palliative care service to have advanced disease were approached. Relatives of consenting patients completed a parallel survey. K-means cluster analysis was used to differentiate between those willing and unwilling to participate. Multivariate logistic regression identified demographic factors predicting willingness.

Results: One hundred and one patients and 100 relatives were included. 92% of patients would participate in studies involving simple interventions, whereas only 26% would consider studies of complex interventions. A similar pattern was observed for relative support. Over 75% of participants expressed altruistic views. Concepts of 'randomisation', 'placebo-control' and 'blinding' deterred about one-half. Many were prepared to complete short questionnaires, accept extra medications, investigations, hospital visits or admissions within a trial context but the possibility of side-effects was a major deterrent. Patient age was the only significant predictor of willingness to participate, with older patients less likely to participate.

Conclusion: Despite the likely absence of individual benefit, many patients appear willing to participate in palliative care research. Trial design and the possibility of side-effects proved very influential in their decision making. Clinical trials in palliative care are more likely to be successful if developed in accordance with the views of patients and their relatives.

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1. Introduction

Evidence-based practice forms an essential part of modern medicine and yet many treatments and interventions used in palliative care have never been evaluated. There are wide variations in clinician practice not only internationally, but within countries and even institutions due to a lack of high-level evidence.[1,2] An example is the uncertainty that surrounds opioid dose equivalence and conversion ratios.[3]

Research in palliative care focuses on symptom control and supportive care for patients and their families. It is widely acknowledged that research in the palliative population is difficult and therefore is often not attempted. Many well-designed randomised controlled trials (RCTs) have failed. The literature is littered with poor studies or studies that have not accrued sufficient numbers of patients.[1,4] Specific challenges include difficulties in recruiting patients of poor performance status, small sample sizes, high attrition rates (up to 60%),[5] rapidly changing clinical situations, limited survival times and the reluctance of health professionals to refer patients for research studies.

It has been argued that research in patients with far-advanced disease is inappropriate as it disrespects a patient's emotional and physical state.[6] Sound evidence is essential to guide decision making,[7] however, and research must be performed in relevant patient groups for it to be clinically applicable.

Research in palliative care requires realistic studies that are practical and achievable. It is necessary to design trials that are acceptable to patients, their families and healthcare professionals. Perceived concerns of patients receiving palliative care have generally been defined by the views of family and healthcare professionals, and often relate to patients with chronic illnesses and not those close to death.[8] Previous studies considering the views of palliative care patients and their relatives have small sample sizes [9,10] and are often qualitative in nature.[8,11]

The aim of this study was to determine if patients with advanced cancer are interested in participation in research that does not involve anti-cancer therapy, particularly in the context of a RCT, and if so, what factors are important in their decisions. What level of inconvenience is tolerable and is willingness to participate influenced by demographic or other factors? As patients with advanced disease are often highly dependant on their relatives or partners, it was important to determine their views to gauge whether they would support trial entry.

2. Patients and methods

2.1. Setting

The study was performed at the Mater Misericordiae Hospital in Brisbane, a university teaching hospital for public patients with a tertiary referral service for oncology. The palliative care service is integrated within the oncology service and provides support and symptom control for patients on the in-patient ward, day oncology unit and in the outpatient department. Patients are seen according to need at any stage of their disease course. Those requiring terminal care are generally transferred to a local hospice facility.

Ethical approval was obtained from the Mater Health Services Human Research Ethics committee.

3. Questionnaire development

A questionnaire was designed through a literature search, focus groups with healthcare professionals (HCPs), patient and relative interviews and pilot studies. This resulted in parallel surveys to assess the views of patients and relatives towards patient participation in palliative care trials, in particular RCTs, which do not involve specific anti-cancer treatment but focus on symptom control.

The final self-administered questionnaires had three sections to assess factors that may affect both the patients willingness to participate (WTP) in RCTs and a relative's decision to support participation (Appendices 1 and 2). Part A considered key issues likely to be important when considering trials. Part B assessed willingness to participate in trials of increasing invasiveness in a hypothetical pain situation. Part C assessed the degree of inconvenience respondents would be prepared to accept or support when participating in a trial. They were asked to score how frequently they would be prepared to concur with a number of trial requirements. Responses were scored on a five point modified Likert scale.

4. Participants

4.1. Patients

Eligible patients were over 18 years of age with a diagnosis of cancer who met the following definition: 'patients with an active, progressive, far-advanced disease for whom prognosis is limited and the focus of care is quality of life'.[12] Patients had to be aware of the advanced state of their disease, have a good understanding of English and cognitive function that allowed fully informed consent. Patients who were receiving chemotherapy had to be aware of its palliative intent. Patients wishing to participate could be assisted by the research team or a relative as long as their responses were not influenced. Patients were excluded if they were too unwell to complete the study requirements. Consecutive patients known to the Mater Palliative Care Service were approached. The absence of a relative did not exclude a patient from the study. Demographic data were collected on all patients by research staff from interview and medical records. Date of death was collected subsequently from hospital records.

4.2. Relatives

Relatives of consenting patients were asked to participate. Carers, other than relatives or partners, were not approached. Eligible relatives were over 18 years of age, able to understand English, have adequate cognitive function and be nominated by consenting patients as a 'significant other'. Relatives self-administered the questionnaire and were requested not to discuss their answers with the patient or other family

members. Relatives were asked to record their own demographic data.

5. Statistical methods

The sample size required for this study was determined assuming multiple regression as the analysis tool. As there were no available estimates of the multiple correlation coefficient (R) for this topic it was anticipated that a small to medium effect size (f^2) would be observed. Consequently, assuming $f^2 = 0.09$, the multiple correlation coefficient was calculated as 0.2873.[13] Using this parameter, as well as an acceptable type I error rate of 0.05 and 11 predictor variables, 197 participants would be required to achieve 80% power. It was therefore decided to involve 100 patients and 100 relatives to give an overall sample size of greater than 197.

In Part A, factors that participants highlighted by responding 'very' or 'quite' interested were considered of importance, whereas factors with 'not really' or 'not at all' responses were considered of less importance. In Part B, participants who answered 'very' or 'quite' willing were considered 'willing' to participate, whereas participants who documented 'not really' or 'not at all' willing were considered 'not willing'. In Part C, willingness to undergo inconvenience was defined as answering at least 'weekly' to each descriptor.

K-means cluster analysis was used to define two clusters according to responses in Parts B and C (willingness and inconvenience tolerated). Responses from Part A were not included as these identified factors of importance rather than a willingness to participate. Univariate analysis was used to gauge the importance of demographic factors. Multivariate logistic regression was used to determine which predictors discriminated between the two groups. Analyses were performed separately for the three cohorts (patients, relatives and all participants combined).

The level of agreement between relatives and patients was calculated using the weighted kappa coefficient of agreement (using the method of 'squared error weights'[14] and the five point Likert scale) for each individual question, part (A, B and C) and for the complete questionnaire. Only the patients who had relatives participating were included, and each relative-patient pair was utilised for calculations (100 pairs in total).

Cluster analyses were performed using SPSS 14 (SPSS Inc., Chicago, Illinois), whilst logistic regression was carried out in SAS 9.1.3 (SAS Institute Inc., Cary, North Carolina). Stata 9.2 (StataCorp, Texas) was used for calculating weighted kappa coefficients.

6. Results

Of the 125 patients screened over a 10 week period (September to November 2006), 20 were excluded. One hundred and five were approached, 101 completed and returned the questionnaire, two refused and two consented but failed to complete the questionnaire (Fig. 1). One hundred and five relatives were nominated, all consented and 100 completed questionnaires were returned. The median number of participating relatives per patient was one (range 0–5); 37 patients had no participating relatives. There were minimal missing data; 102 of 6030 (1.69%) questions were unanswered. Power was reduced to 59% when examining the relative subgroup, but increased to 86% when analysing patients only.

Demographic data are shown in Table 1. There was a trend favouring females in the patient group ($p = 0.091$) reflecting the frequency of breast and gynaecological cancers: breast (23), gastrointestinal (25), gynaecological (20), lung (12), prostate (10), skin (5), renal (5) and brain (1) (data not shown). Most patients were aged 50–69 years (52.5%) and had not received higher education (79.2%) (data not shown). Relatives were generally younger ($p < 0.001$), of better performance status ($p < 0.001$) and had achieved a higher level of education than patients ($p < 0.001$). There was no difference in the proportion of patients and relatives with previous research experience ($p = 0.469$) (Table 1).

The importance (as determined by the degree of interest in participation) of individual trial factors is shown in Fig. 2 and Appendix 3. For example, over three quarters of participants (82% of patients and 76% of relatives) expressed altruistic views in that they were interested in studies that may help others and not themselves. The proportion of participants willing to participate, or to support participation, in trials of increasing invasiveness is shown in Fig. 3 and Appendix 4. The proportion willing to participate or support trials was directly related to the invasiveness of the trial, i.e. as trials became more complex or had the possibility of side-effects, fewer were willing to participate. For example, approximately three quarters were willing to participate or support participation in a trial of an oral analgesic with no known side-effects, but this dropped to approximately one quarter if there were side-effects. The frequency with which participants

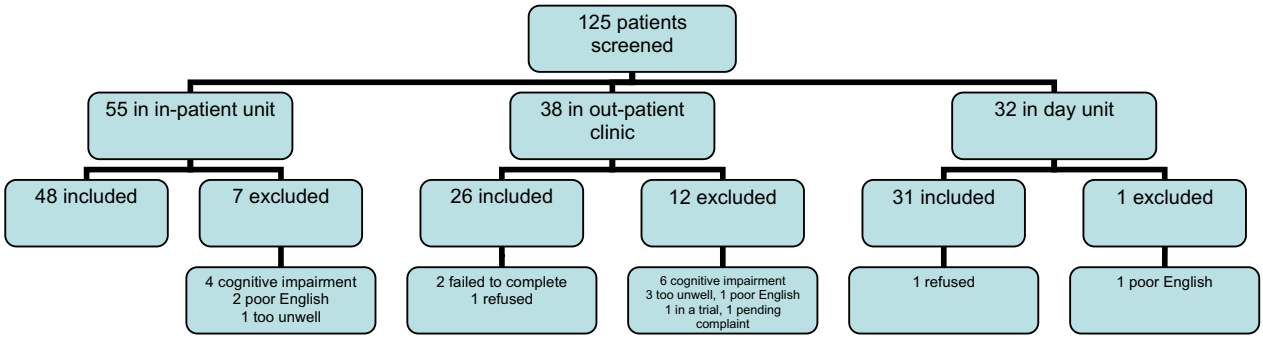

Fig. 1 – Patients screened for study.

Table 1 – Demographic data

	Number of patients	Number of relatives	Significance
Gender			
Male	42	34	0.309
Female	59	66	
Age*			
<50	17	38	<0.001
50+	84	60	
Missing data	0	2	
ECOG status*			
0–2	80	100	<0.001
3–4	21	0	
Previous research experience			
Yes	41	35	0.469
No	60	64	
Missing data	0	1	
Level of education*			
Primary school/minimum leaving age	59	33	<0.001
Senior school/university	42	67	
Time since cancer diagnosed			
<1 year	54		
⩾1 year	46		
Missing data	1	–	
Time known to palliative care team prior to questionnaire completion			
<1 month	81		
⩾1 month	20	–	
Estimated prognosis (by researchers)			
<3 months	54	–	
⩾3 months	47	–	
Time from survey to death			
<3 months	30	–	
⩾3 months	71	–	
Site			
In-patient unit	48	54	0.399
Out-patient clinic/day unit	53	46	
Relationship to patient			
Spouse/partner	–	40	
Child	–	30	
Parent	–	5	
Other relative	–	25	

* Factors for which there was significant difference between patients and relatives. Dichotomous groupings for demographic predictors were: age (<50 years versus ⩾50 years), gender (M versus F), performance status (ECOG 0–2 versus 3–4), educational level (primary/minimum leaving age versus high school/post school), previous trial experience (Y versus N), site (in-patients versus out-patient/day unit), time from diagnosis of cancer (<1 year versus ⩾1 year), time known to palliative care (<1 month versus ⩾1 month), estimated prognosis (<3 months versus ⩾3 months), time from survey to death (<3 months versus ⩾3 months) and status (patient versus relative).

were prepared to undergo or support a number of trial requirements, and therefore undergo inconvenience, is shown in Appendix 5. The percentage willing to undergo each inconvenience at least weekly is demonstrated in Fig. 4. For example, many patients (47%) and relatives (65%) were prepared to make extra visits to the hospital at least once a week, with 37% and 44%, respectively, prepared for the patient to spend a night in hospital at least weekly.

Cluster analysis was performed on the data for patients and relatives separately, as well as for all participants. In all cases, the cohort was successfully classified into two groups corresponding to WTP and not WTP. For all groups there were approximately equal numbers of cases in each cluster with large distances between cluster centres, indicating dissimilar groups (Appendix 6). Univariate analysis determined that no demographic factors were related to WTP for patients. There was a trend towards 'time since diagnosis' predicting WTP for relatives ($p = 0.051$). Using multivariate logistic regression (Table 2), age was the only patient factor that discriminated between the clusters ($p = 0.0497$) with older patients less likely to participate in research. For relatives, gender ($p = 0.105$) was the only predictor that approached statistical significance as a discriminating factor, with males more likely to support participation. When all data were combined, no variables could predict participation. The inclusion of Part A in the analysis did not change the outcome.

For the agreement analysis there were 64 patients who had relatives participating (range 1–5 relatives) and each relative-patient pair was included for analysis (100 pairs). There was

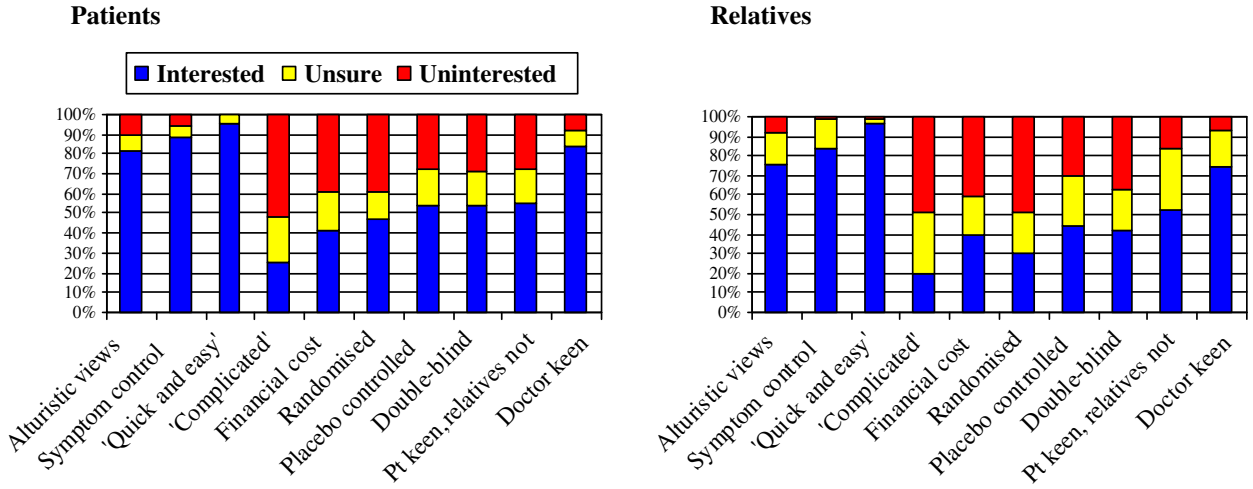

Fig. 2 – Trial factors considered important by patients and relatives.

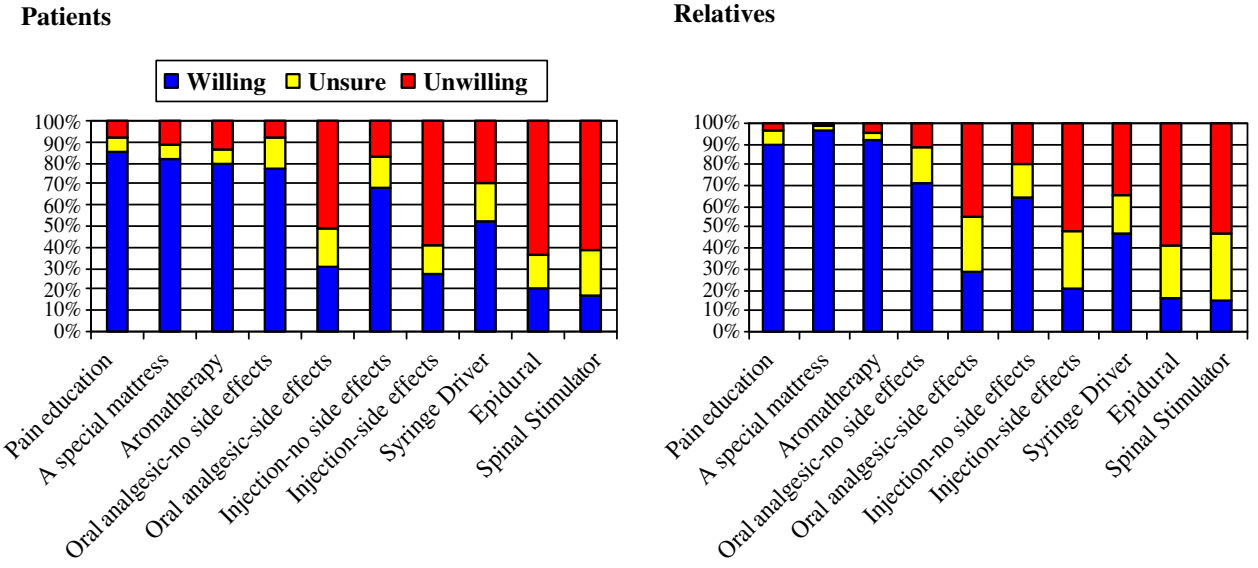

Fig. 3 – Interest in trials of increasing invasiveness.

statistically significant agreement between relatives and patients in 12 of the 30 questions (indicating that there was more agreement than simply by chance). An overall kappa agreement value of 0.348 ($p < 0.001$) was obtained. The level of agreement was significant for each part with kappa equalling 0.292, 0.404 and 0.332, respectively, for parts A, B and C ($p < 0.001$ for all). The question with the highest level of agreement ($\kappa = 0.414$) was that relating to taking extra tablets, whilst that with the lowest level ($\kappa = -0.202$) was the question relating to a relative's reaction to trial participation if the patient was willing but they were not. However, it must be noted that values of kappa less than 0.4 indicate poor agreement.[14] This level of agreement was only reached by one individual question and part B.

7. Discussion

There has been controversy amongst healthcare professionals about the appropriateness of involving patients with advanced disease in research, especially when the patients themselves may not directly benefit. In this survey, over three quarters of patients and relatives expressed altruistic views in that they were interested in participating in, or supporting a study that would be unlikely to help the patient but might help others in the future. This is consistent with findings from other studies.[8,9,15,16] 'Contributing to others' has been found to be one of the key aspects of a good death.[16] Similarly, contributing to service change was seen as a legacy to others by patients approaching the end of life.[17] Patients are often willing to participate in research as a meaningful way to give back to the community,[15] or to find some meaning in their death through the advancement of knowledge and improvements in care for others.[9]

A fundamental difference between trials in oncology and those in palliative care is that the end-points in the former may be tumour response and prolonged survival whereas those in the latter are more likely to relate to improvement in symptom control and/or quality of life. The majority of

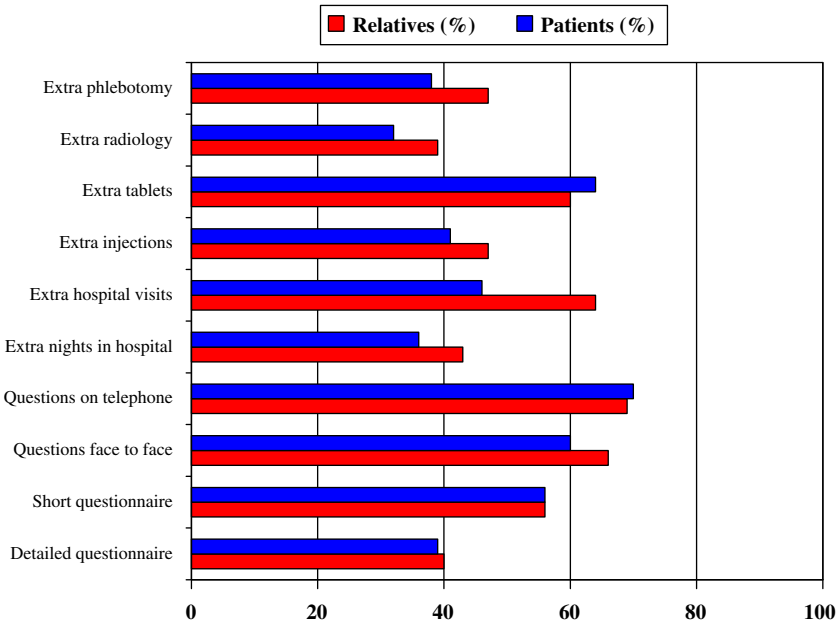

Fig. 4 – Percentage of participants willing to undergo (or support) each potential inconvenience at least weekly.

participants in this survey were interested in studies of symptom control that would have no impact on cancer progression, suggesting an interest in trials that may improve quality and not necessarily quantity of life.

The opinions of others are often important when considering trial participation. This survey suggests that many relatives would influence, and potentially deny, a patient's choice to participate. Only 55% of interested patients would participate in a study if their relatives were not supportive, and only 51% of relatives would continue to support a patient's decision to participate in a trial if they were not keen for them to do so. Furthermore, whilst there was a degree of agreement overall between relative and patient pairs, the level of agreement did not reach significance in 18 of the 30 questions. This has concerning implications with respect to patient autonomy. In a previous study of consent by proxy, 31% of relatives who believed a patient would refuse to participate in a trial still gave consent in apparent opposition to the patient's wishes.[18]

The opinion of the treating doctor was important to the majority of participants with respect to trial participation. Oncology patients have been shown to be attracted by the opportunity of treatment from a specialist and being closely monitored as part of participation in clinical research.[19] This has implications in those situations where the patient is in a dependant position with respect to future treatment. It has been suggested that research officers approaching patients should act independently of treating teams. Others have found that patients preferred to be approached by a member of their treating team as they appreciated their relationship with their doctors and were unwilling to deal with independent research staff.[8]

There has been debate about the ethics of placebo-controlled trials in palliative care.[1,20] The concepts of random allocation, placebo controls and double-blind trial designs were a deterrent in this study in 40%, 28% and 29% of patients, respectively, and many were unsure. The concept of randomisation has been shown to be 'off putting' for oncology patients considering trials.[21,22] Moreover, many cancer patients do not have a good understanding of the need for RCTs or the manner and safe-guards with which they are conducted.[23] There remains a concern as to the level of understanding of these principles in the palliative care population, and points to the need for patient education, for example by the provision of 'understanding clinical trials' leaflets [24] or creating a culture of clinical trials as the norm within units.

Financial cost to the patient was the major deterrent to trial participation in this study. This issue must be addressed in the design of all studies to improve recruitment to trials and minimise additional participant burden.

There was a striking correlation between the invasiveness of trial interventions and willingness to participate in the hypothetical pain study. Whilst over 80% of all respondents would support simple non-drug trials (pain education, special mattress and aromatherapy), less than 20% would support a trial of an epidural infusion or spinal stimulator. This trend was consistent in both patients and relatives. This finding is consistent with a previous study in palliative care that found patients to be less interested in invasive studies.[9]

The potential for side-effects was highlighted as a factor of great importance. The majority were willing to participate in trials of tablets or injections with no known adverse effects, but not when there was the possibility of side-effects. In contrast, a study of cancer patients receiving initial chemotherapy showed that most were willing to accept intensive chemotherapy with significant side-effects for a very small chance of benefit.[25]

A previous review of recruitment concluded that trials of longer than one month duration were generally not feasible in a palliative care population.[26] When designing a trial, it is important to consider the level of inconvenience patients

Table 2 – Results of multivariate logistic regression modelling willingness to participate

Factor	Patients		Relatives		All participants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Status						
Patient	–	–	–	–	1.00	
Relative	–	–	–	–	1.15	(0.59, 2.24)
Site						
In-patient	1.00		1.00		1.00	
Out-patient/day unit	1.66	(0.65, 4.29)	1.43	(0.51, 4.03)	1.42	(0.73, 2.76)
Previous research						
Yes	1.00		1.00		1.00	
No	0.81	(0.33, 2.02)	0.49	(0.19, 1.28)	0.63	(0.34, 1.16)
Age						
<50 years	1.00		1.00		1.00	
⩾50 years	0.30	(0.09, 1.00)	1.38	(0.55, 3.48)	0.69	(0.34, 1.40)
Sex						
Male	1.00		1.00		1.00	
Female	0.85	(0.34, 2.14)	0.44	(0.16, 1.19)	0.66	(0.36, 1.21)
ECOG status						
0-2	1.00		1.00		1.00	
3-4	2.09	(0.65, 6.71)	1.22	(0.40, 3.74)	1.36	(0.63, 2.92)
Education						
Primary/minimum	1.00		1.00		1.00	
Senior/TAFE/University	0.77	(0.32, 1.88)	0.71	(0.27, 1.86)	0.73	(0.39, 1.39)
Time since diagnosis						
<1 *year*	1.00		1.00		1.00	
⩾1 *year*	1.06	(0.42, 2.66)	2.11	(0.84, 5.33)	1.45	(0.79, 2.68)
Time in palliative care						
<1 month	1.00		1.00		1.00	
⩾1 month	0.55	(0.18, 1.65)	0.93	(0.25, 3.42)	0.79	(0.36, 1.74)
Estimated prognosis						
<3 months	1.00		1.00		1.00	
⩾3 months	0.89	(0.30, 2.62)	0.49	(0.12, 1.95)	0.70	(0.32, 1.56)
Time to death						
<3 months	1.00		1.00		1.00	
⩾3 months	0.76	(0.25, 2.34)	1.02	(0.24, 4.25)	0.68	(0.29, 1.58)

are willing to tolerate. In this survey, many patients and relatives were prepared to make extra visits to the hospital, spend a night in hospital, answer questions by telephone or face-to-face and complete questionnaires weekly. Approximately, one-third of patients were willing to undergo weekly blood tests or radiology. Almost two-thirds were prepared for extra tablets and over 40% for injections, at least weekly. Relatives often seemed more prepared for the patient to undergo inconvenience than were the patients themselves, again highlighting the difficulties with proxy consent. This information provides guidance as to the level of inconvenience that patients and relatives are willing to tolerate, and should be considered when designing future trials.

Many patients and relatives in this study had a low educational level. Whilst this may be a reflection of the advanced median age of our patient population, it also highlights the importance of providing information at an appropriate level. These patients are by definition unwell with potential difficulties in concentration and understanding complex trial-related information. Consideration should be given to shortened and simplified patient information and consent forms, in order to facilitate participation.[27]

Demographic and other factor analyses revealed few predictors of willingness to participate in RCTs. There was a loss of power in the analysis when examining the relatives only. Age was the only factor that was a predictor for patients, with those over 50 years less likely to participate. This is consistent with the findings from other studies.[28–30] No factor predicted willingness for relatives, although there was a trend towards greater support from males. This survey argues against 'gatekeeping' (7); patients should not be shielded from entering trials by well meaning health professionals on the basis of other factors such as educational background or performance status.

This study is strengthened by the high participation rate; of 105 consecutive eligible patients, only four did not participate. This is therefore likely to be a true reflection of the population under study. A weakness is the potential discrepancy between what participants agree to in theory and what they will do in practice. In the hypothetical trial presented related to pain management; not all patients had pain and this might have affected their response. Similarly, the trials were presented in a simplistic form. Patients would require much more information before making a fully informed decision.

This study only included patients with malignant disease in a hospital setting. Only a small number of patients surveyed were in the terminal phase, most were of reasonable performance status and some were still undergoing specific

anti-cancer treatment. The results from this survey are not necessarily applicable to the wider palliative care population or to those with non-malignant disease. It did however encompass those likely to be well enough to be included in clinical trials of supportive or palliative care.

8. Conclusion

This survey has confirmed findings from other studies. Patients with advanced cancer are interested in participating in RCTs that focus on symptom control and not cancer treatment, and their relatives are frequently willing to support participation. It refutes the suggestion that this patient group should not be involved in research as many have altruistic views towards research participation.

This survey has highlighted methodological factors that need to be considered in trial design in order to make RCTs more acceptable to patients and their relatives. It suggests that many cancer patients are highly influenced by the perceived complexity or invasiveness of an intervention or treatment and the possibility of side-effects. It demonstrated that patients are prepared to accept some inconvenience but should be protected from additional financial burden. Advanced patient age is the only factor that predicts an unwillingness to participate. To encourage trial participation, careful explanation of the trial should be given without coercion and where appropriate, the patient's family should be involved. The development of trials that are more acceptable to patients and their relatives should increase recruitment rates and completion of trials.

The necessity for consumer involvement in the design and conduct of controlled trials is well recognised. Such involvement is likely to improve the relevance to consumers of the questions addressed and the results obtained.[31,32] If the results of this survey are used to guide future trial design, it might increase the likelihood of successfully completing RCTs and thus decrease the uncertainty surrounding many of the interventions used in palliative care.

Conflict of interest

None declared

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2008.05.003.

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